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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,874	WANG ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-9,14,16,17,19,21-23,39,43-46,51,53-55,57,87,89 and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23,51,87,89 and 90* is/are allowed.

6)☒ Claim(s) *6-9,14,16,17,19,21,22,39,43-46,53-55 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1-5, 10-13, 15, 18, 20, , 24-38, 40-42, 47-50, 52, 56, 58-86, 88 and 91 have been cancelled, and claims 6-9, 14, 16-17, 19, 21-23, 39, 43-46, 51, 53-55, 57, 87, 89 and 90 have been amended. Claims 6-9, 14, 16-17, 19, 21-23, 39, 43-46, 51, 53-55, 57, 87, 89 and 90 are under examination.

It is noted that claims 87 and 89-90 were indicated as allowable and claims 6-9, 14, 16-17, 19, 21-23, 39, 43-46, 51, 53-55 and 57 were previously indicated as allowable if written in independent form. However, upon further consideration, new grounds of rejection have been applied below. Prosecution of this Application is reopened.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-85 and 91 have been canceled; therefore the rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is moot.

Claims 22 and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The claims recite the phrase "said portions being defined by one or two restriction endonuclease recognition sites, wherein said portions are defined by the presence of a BcgI restriction endonuclease recognition site". The claims encompass an embodiment in which BcgI is one of two restriction endonucleases used to define the genome portions. The instant specification discloses an alternative embodiment in which BcgI is the only restriction endonuclease used (paragraph 0020) and discloses that BcgI fragments contain sufficient information to identify the genomic location from which they were derived (paragraph 0043). The specification does not disclose or contemplate use of BcgI in combination with another endonuclease to define the genome portion. Therefore, a method wherein "said portions being defined by two restriction endonuclease recognition sites, wherein said portions are defined by the presence of a BcgI restriction endonuclease recognition site" constitutes impermissible new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-9, 21, 43-46 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 6,498,013 (Velculescu et al, of record), filed 7/27/2001, in view of Dunn et al (Nov. 4, 2002, of record) as evidenced by Yoshida et al (U.S. Patent App. Publication No. 2002/0147549, filed 10/26/2001). This is a NEW rejection.

Applicants claim a method of karyotyping a genome of a test eukaryotic cell by generating a population of sequence tags defined by restriction endonuclease sites from the genome of the test eukaryotic cell, enumerating the sequence tags and comparing the number of sequence tags to the number of sequence tags calculated to be present in the human genome to determine karyotypic differences or abnormalities. Applicants claim a method of karyotyping a genome by enumerating pieces of a genome of a test cell and enumerating the pieces within a plurality of windows to determine karyotypic differences or abnormalities. Applicants claim these methods wherein the window spans about 40 kB, or about 200 kB or about 600 kB or about 4 Mb. Applicants also claim a method of karyotyping a genome of a test eukaryotic cell wherein recognition or cleavage by the first restriction endonuclease is sensitive to DNA methylation.

Velculescu et al teach a method of serial analysis of gene expression (longSAGE) for human genomic data comprising analysis of long sequence tags defined by endonuclease recognition sites that were generated from human mRNA for the purpose of quantitative comparison of expressed transcripts in a variety of normal and disease states (see column 3, lines 1-5, for example). Velculescu et al generate dimerized tags comprising two sequence tags from a eukaryotic cell from endonuclease recognition sites consisting of 17-21 nucleotides extending from the restriction

endonuclease recognition sites which are concatamerized and cloned for sequencing (see column 2, lines 40-67, for example). Velculescu et al teach that the sequence tag data generated from the test cell is then compared to known human genome data (see column 12, lines 5-15 and lines 31-35) and matched to the corresponding genomic database (see column 12, lines 59-67 and column 13, lines 1-3, for example). Velculescu et al teach that the method can be used for comparison of gene expression between pathological and normal tissue, which is useful for identifying diagnostically, prognostically and therapeutically important genes (see column 22, lines 31-40, for example) which meets the limitation of determining a difference in sequence tags in a test cell compared to a normal cell to discover a karyotypic difference. Velculescu et al exemplify sequence tags from colon cancer cells (see column 7, lines 32-35, for example).

Velculescu et al teach that computer analysis of human pancreas transcripts revealed 84,300 sequences. Velculescu et al teach further analysis was performed using a SAGE database analysis program set to include only sequences noted as "RNA" in the locus description and to exclude entries noted as "EST", which resulted in a reduction of the 84,300 sequences to 13,241 sequences. Velculescu et al analyzed this 13,241 subset of sequences using NlaIII as the restriction enzyme and indicated that 4,127 tags were unique while 1,511 tags were found in more than one entry. Velculescu et al suggested that 5381 of the 9 bp tags were unique to a transcript or highly conserved transcript family. Further, Velculescu et al exemplify the method of serial analysis of gene expression (longSAGE) method and only analyze the first 1000

tags (see column 15, lines 30-67, for example). Analysis of 1000 tags out of ~5381 tags is enumeration of **~18%** of the sequence tags calculated to be present. Therefore, Velculescu et al does teach a method wherein less than 100 % of the sequence tags calculated to be present in the genome of the eukaryotic cell are enumerated. Velculescu et al do not teach production of sequence tags from genomic DNA.

Dunn et al teach a method of karyotyping a genome of a test eukaryotic or prokaryotic cell by generating a library of sequence tags defined by endonuclease recognition sites including NlaIII, concatamerizing the sequence tags for sequencing and numbering (see page 1757, left column, in particular). Dunn et al also teach that the number of sequence tags generated from the test cell is compared to the number of sequence tags calculated to be present in a reference cell (see page 1759, left column, 2nd and 3rd paragraph and right column, 1st full paragraph). In addition, Dunn et al teach that comparison of the number of sequence tags between the test cell and the reference cell revealed that some sequence tags that were predicted to be present in the reference cell were not present in the test cell, and were deletions or rearrangements of the test cell genome (see page 1760, left column, for example), which meets the limitation of a difference in the number of sequence tags present in the population of sequence tag between a test cell and a reference cell indicating a karyotypic difference.

Specifically, Dunn et al teach that tags were sequenced and matched to the reference genome of *Yersinia pestis,* which is 4.7 Mb from which restriction nuclease cleavage sites had been determined *in silico.* Dunn et al teach that a population of fragments produced from cleavage with BamHI-NlaIII or NotI-NlaIII would be less than

21 bp long and all other fragments would be 21 bp in length. Dunn et al teach that if only 21 bp tags are considered, than the NotI-NlaIII library should sample approximately 2.4 kb of the *Y. Pestis* sequence, whereas the BamHI-NlaIII library would sample about 26kb (see page 1758, right column, 2nd paragraph and page 1759, left column, 3rd paragraph). It is noted that the instant specification does not provide a limiting definition of the word "about". Therefore the limitations of about 40 kb, about 200kb, about 600 kb and about 4 Mb will been given the broadest reasonable interpretation, wherein about can encompass a difference of 50kb, 100 kb, 500kb, etc. Therefore the 4.7 Mb *Y. Pestis* genome, and the BamHI-NlaIII library providing 26 kb, meets the limitations of a window of "about" 40 kb, about 200kb, about 600 kb and about 4 Mb.

It would have been obvious to the skilled artisan at the time the invention was made to modify the method of Velculescu et al to examine genomic DNA from eukaryotic human test cells to compare to the number of sequence tags that are predicted to be present in the human genome, because Dunn et al teach the use of eukaryotic cells and that the longSAGE method can be easily modified to obtain genomic sequence tags by starting with genomic DNA fragments rather than poly(A)+ derived cDNA (see page 1763, left column, 1st full paragraph). Velculescu et al teach that RNA transcript expression can be examined using a method very similar to the method of Dunn et al comprising generating sequence tags with endonuclease activity and creating dimers of the sequence tags for further concatamerization, sequencing and analysis. Although Dunn et al may not contemplate the use of dimers; Velculescu et al teach that the advantage of using ditags is a means to eliminate potential distortion

introduced by the PCR amplification step on monomeric tags (see column 6, lines 8-17, for example). The motivation to examine genomic DNA is the expected benefit of the ease and speed of the method of Dunn et al to determine karyotypic difference between genomic sequence tags of a test eukaryotic cell and the human genome. There is reasonable expectation of success since the methods have worked previously in the cited techniques. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore Velculescu et al in view of Dunn et al render obvious a method of karyotyping a genome wherein the window spans about 40kb, about 200kb, about 600 kb or about 4 Mb to indicate a karyotypic difference (**claims 6-9**).

As written, claims 43-46 are very similar to claims 6-9. Claims 43-46 recite the phrase "sequence tags calculated to be present in the genome" in line 10, while claims 6-9 recite the phrase "sequence tags determined for a genome". The instant specification does not appear to provide limiting definitions that would differentiate between "calculated" and "determined". Dunn et al have determined *in silico* the numbers of cleavage sites for NotI, BamHI and NlaIII and have predicted numbers of tags of a particular length (see page 1759, Table I). Absent evidence to the contrary, Dunn et al meet the limitation of calculating a number of a plurality of sequence tags to be present in the genome.

It should be noted that the Applicants do not specifically define karyotypic abnormality in the specification and therefore karyotypic abnormality will be interpreted as claimed to mean a difference in the number of sequence tags by insertion or deletion between a test eukaryotic cell and the human genome. As discussed above, Dunn et al teach that comparison of the number of sequence tags between the test cell and the reference cell revealed that some sequence tags that were predicted to be present in the reference cell were not present in the test cell. The deletions were in a region that comprised gene encoding virulence genes involved in iron acquisition from a host of the *Y.pestis* (see page 1760, left column, for example), which meets the limitation of a difference in the number of sequence tags present in the population of sequence tag between a test cell and a reference cell indicating a karyotypic abnormality. Therefore Velculescu et al in view of Dunn et al also render obvious a method of karyotyping a genome wherein the window spans about 40kb, about 200kb, about 600 kb and about 4 Mb to indicate a karyotypic abnormality (**claims 43-46**).

Dunn et al teach the use of BamHI and NotI, to initially digest genomic DNA, which define the ends of the cleaved fragments by their characteristic cleavage sequences (see page 1757, Figure 1, for example). Yoshida et al teach that Not I is sensitive to methylation (se paragraph 0153, in particular). Although Dunn et al do not teach that NotI is sensitive to DNA methylation; it is an inherent property of NotI. Therefore, Velculescu et al and Dunn et al render obvious a method of karyotyping a genome of a test eukaryotic cell wherein recognition or cleavage by the first restriction endonuclease is sensitive to DNA methylation (**claims 21 and 56**).

Claims 16 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Velculescu et al (U.S. Patent 6,498,013, of record), in view of Dunn et al (of record) and further in view of Mohammed et al (U.S. Patent App. Publication No. 2003/0124584, filed 9/27/2002. This is a NEW rejection.

Applicants claim a method of karyotyping a genome of a test eukaryotic cell wherein the test cell is a cell of a person with a hereditary disorder.

The teachings of Velculescu et al and Dunn et al have been detailed in the above rejection. As detailed above, Velculescu et al in view of Dunn et al render obvious a method of karyotyping a genome. Neither Velculescu et al or Dunn et al specifically teach a test cell of a person with a hereditary disorder.

Mohammed et al teach methods to determine genetic mosaicism using a genetic DNA microarray based comparative genomic hybridization for human cells (see paragraphs 0002 and 0014). Mohammed et al teach that the inventive method can be used to determine the karyotype of a cell population. Mohammed et al teach that specific diseases and conditions have characteristics karyotypes, and that characterization of a cell population can be used to diagnose, detect or prognose these diseases or conditions (see paragraph 00540055). Mohammed et al teach a method comprising a karyotypic analysis of cells with normal karyotypes that have no known chromosomal aberrations for comparison to the test cell (see paragraph 0043, for example). Mohammed et al also teach that karyotypes can be helpful in situations when the causality, diagnosis or prognosis of a condition is associated with a genetic defect such as an inherited condition. In this case, the amount or degree of different

subpopulation comprising different karyotypes can be helpful in formulating a treatment plan or prognosis (see paragraph 0116, in particular).

It would have been obvious to the skilled artisan at the time the invention was made to modify the method rendered obvious by Velculescu et al and Dunn et al and karyotype a test cell of a person with an hereditary disorder (i.e. an inherited condition) because Mohammed et al teach that karyotypes are useful to diagnose, detect or prognose these diseases. The motivation to determine a karyotype using a test cell from a person with a hereditary disorder would be the expected benefit of being able to formulate a treatment plan specific for that individual with a particular karyotypes. There is a reasonable expectation of success in being able to perform a karyotyping method with a test cell from a person with a hereditary disorder because it is a common practice and has worked previously in the cited reference. Therefore Velculescu et al in view of Dunn et al further in view of Mohammed et al render obvious a method of karyotyping a genome of a test cell of a person with a hereditary disorder to determine a karyotypic difference between a test cell and a reference cell (**claim 16**).

As written, claim 16 is very similar to claim 53. Claim 53 recites the phrase "sequence tags calculated to be present in the genome" in line 11, while claim 16 recite the phrase "sequence tags determined for a genome". The instant specification does not appear to provide limiting definitions that would differentiate between "calculated" and "determined". Dunn et al have determined *in silico* the numbers of cleavage sites for NotI, BamHI and NlaIII and have predicted numbers of tags of a particular length (see page 1759, Table I). Absent evidence to the contrary, Dunn et al meet the

limitation of calculating a number of a plurality of sequence tags to be present in the genome.

It should be noted that the Applicants do not specifically define karyotypic abnormality in the specification and therefore karyotypic abnormality will be interpreted as claimed to mean a difference in the number of sequence tags by insertion or deletion between a test eukaryotic cell and the human genome. An inherited disorder detectable by karyotyping meets the limitation of a karyotypic abnormality. Therefore Velculescu et al in view of Dunn et al further in view of Mohammed et al render obvious a method of karyotyping a genome of a test cell of a person with a hereditary disorder to determine a karyotypic abnormality between a test cell and a reference cell (**claim 53**).

Claims 17 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Velculescu et al (U.S. Patent 6,498,013, of record), in view of Dunn et al (of record) and further in view of Davis et al (U.S. Patent No. 5,391,480, 2/21/1995. This is a NEW rejection.

Applicants claim a method of karyotyping a genome of a test eukaryotic cell wherein the test cell is a cell of a person with an infectious disease.

The teachings of Velculescu et al and Dunn et al have been detailed in the above rejection. As detailed above, Velculescu et al in view of Dunn et al render obvious a method of karyotyping a genome to indicate karyotypic differences or abnormalities. Neither Velculescu et al or Dunn et al specifically teach method comprising a test cell of a person with an infectious disease.

Davis et al teach a method for determining the incidence of a particular nucleotide at a specific locus on a strand of DNA that has a known sequence. Davis et al teach that it is useful to determine an individual's genotype at a test locus since genotypes can relate to the existence of an allele or mutation responsible for a disease state (see column 4, lines 55-65, for example). Davis et al disclose that there are known disease states that are caused by such variation at single nucleotide position on a strand of DNA. Davis et al teach that usefulness of detecting such variation includes karyotyping and diagnostics of infectious disease (see column 1, lines 16-25, for example).

It would have been obvious to the skilled artisan at the time the invention was made to modify the method rendered obvious by Velculescu et al and Dunn et al and karyotype a test cell of a person with an infectious disease because Davis et al teach that some disease state are caused by small variations on a DNA strand. The motivation to test a cell from a person with an infectious disease would be the expected benefit of being able to diagnose the infectious disease. There is a reasonable expectation of success in being able to perform a karyotyping method with a test cell from a person with an infectious disease because it has worked previously in the cited reference. Therefore, Velculescu et al in view of Dunn et al further in view of Davis et al render obvious a method of karyotyping a genome of a test cell of a person with a an infectious disease to determine a karyotypic difference (**claim 17**).

It should be noted that an altered allele detectable by karyotyping meets the limitation of a karyotypic abnormality. Therefore Velculescu et al in view of Dunn et al

further in view of Davis et al render obvious a method of karyotyping a genome of a test cell of a person with an infectious disease to determine a karyotypic abnormality between a test cell and a reference cell (**claim 54**).

Claims 19 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Velculescu et al (U.S. Patent 6,498,013, of record), in view of Dunn et al (of record) and further in view of Winkfein et al (U.S. Patent No. 5,663,048, 9/2/1997). This is a NEW rejection.

Applicants claim a method of karyotyping a genome of a test eukaryotic cell wherein the first restriction endonuclease is SacI. It is noted that as claims 19 and 55 are written, there is no specific function to SacI as the first restriction endonuclease besides defining portions of the genome of the test eukaryotic cell.

The teachings of Velculescu et al and Dunn et al have been detailed in the above rejection. Dunn et al teach the use of BamHI, NotI, NlaIII to digest genome DNA, which define the ends of the cleaved fragments by their characteristic cleavage sequences. Velculescu et al in view of Dunn et al render obvious a method of karyotyping a genome. Neither Velculescu et al or Dunn et al specifically teach a method wherein the first restriction endonuclease is SacI.

Winkfein et al contemplate methods of determining gender of embryos by karyotyping fetal cells, as well as methods of hybridization with Y chromosome specific probes (see column 2, lines 40-45, and column 3, lines 21-35 for example). Winkfein et al teach preparation of genomic DNA for methods of detection of Y chromosome

specific sequences in which genomic DNA is digested with SacI restriction endonuclease (see column 9, lines 50-56 for example).

It would be obvious to the skilled artisan at the time the invention was made to modify the methods rendered obvious by Velculsecu et al and Dunn et al and use SacI as a first restriction endonuclease because Winkfein et al teach that SacI is useful to cleave genomic DNA in methods to detect hybridization of specific sequences of DNA. SacI is a restriction endonuclease that is well known in the art. It would be obvious to substitute SacI in the place of BamHI or NotI, as taught by Dunn et al as a first restriction endonuclease that defines the ends of portions of the cleaved genome because the substitution of one restriction endonuclease known to cleave genomic DNA for another restriction endonuclease would have yielded predictable results to the skilled artisan at the time of the invention.

Therefore Velculescu et al in view of Dunn et al further in view of Winkfein et al render obvious a method of karyotyping a genome of a test cell, wherein the first restriction nuclease is SacI (**claims 19 and 55**).

Claims 22 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Velculescu et al (U.S. Patent 6,498,013, of record), in view of Dunn et al (of record) and further in view of Israel et al (U.S. Patent No. 5,981,190, of record). This is a NEW rejection.

Applicants claim a method of karyotyping a genome of a test eukaryotic cell wherein the portion of the genome are defined by the presence of a BcgI restriction

endonuclease recognition site flanked by 12 nucleotides at either end. It is noted that as claims 22 and 39 are written, there is no specific function to BcgI as the first restriction endonuclease besides defining portions of the genome of the test eukaryotic cell.

The teachings of Velculescu et al and Dunn et al have been detailed in the above rejections. Dunn et al teach the use of BamHI, NotI and NlaIII to digest genome DNA, which define the ends of the cleaved fragments by their characteristic cleavage sequences. Velculescu et al in view of Dunn et al render obvious a method of karyotyping a genome. Neither Velculescu et al or Dunn et al specifically teach a method wherein portions of the genome are defined by the presence of a BcgI restriction endonuclease recognition site flanked by 12 nucleotides at either end.

Israel et al teaches a method for formation of dimers from genomic DNA of human eukaryotic cells (see column 3, lines 52-59, for example). Israel teaches that genomic DNA can be fractionated into smaller fragments by cleaving with enzymes that cleave DNA based on methylation state or condensation state. The smaller DNA fragments are then cleaved with an anchoring enzyme, ligated on to a linker sequence that includes a Type IIS endonuclease recognition site and then cleaved with a Type IIS endonuclease (second tagging enzyme). Israel et al teach that BcgI is an exemplary enzyme (see column 5, lines 9-11 and column 11, lines 35-45, for example).

It would be obvious to the skilled artisan at the time the invention was made to modify the methods rendered obvious by Velculsecu et al and Dunn et al and use BcgI to define the genome portions because Israel et al teach that BcgI is useful to cleave genomic DNA. BcgI is a restriction endonuclease that is well known in the art. It would

be obvious to substitute BcgI in the place of BamHI or NotI, as taught by Dunn et al as a restriction endonuclease that defines the ends of portions of the cleaved genome because the substitution of one restriction endonuclease known to cleave genomic DNA for another restriction endonuclease would have yielded predictable results to the skilled artisan at the time of the invention.

Therefore Velculescu et al in view of Dunn et al further in view of Israel et al render obvious a method of karyotyping a genome of a test cell, wherein the first restriction nuclease is SacI (**claims 22 and 39**).

Conclusion

Claims 23, 51, 87 and 89-90 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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Laura McGillem Mitchell, PhD
Examiner
8/22/2007

/Joseph Woitach/
Joseph Woitach
SPE 1636